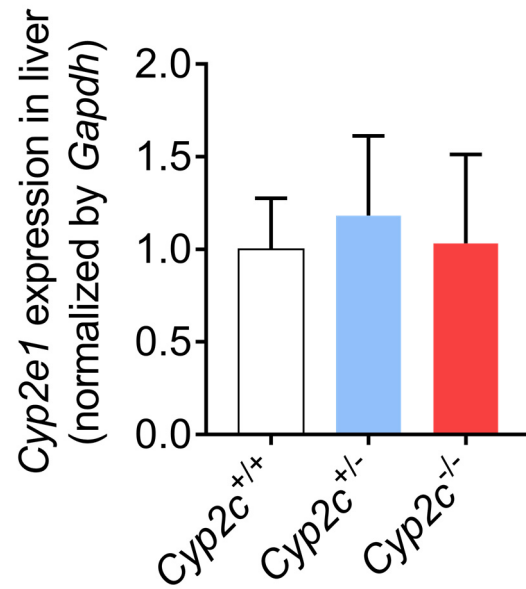
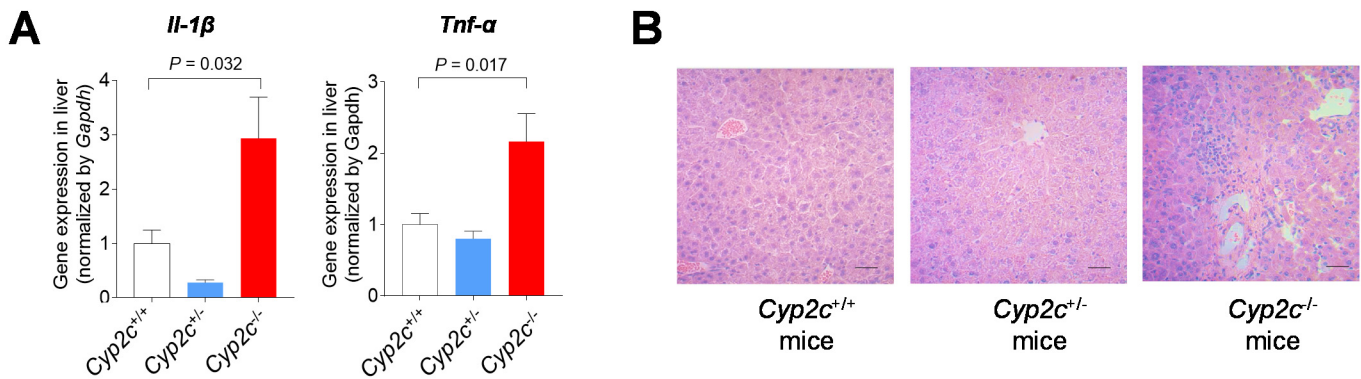


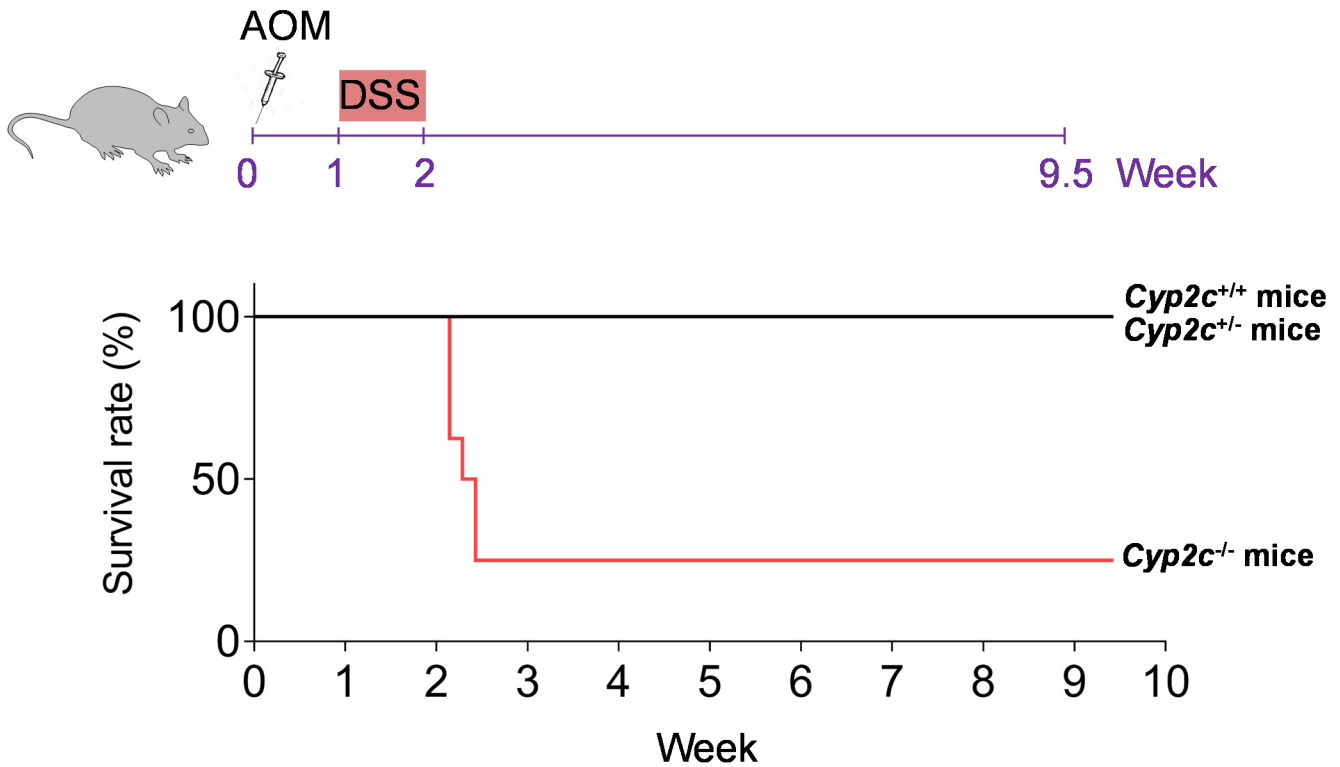
**Figure S1.** CYP monooxygenases are overexpressed in human colon cancer cells. (A) Gene expression of *CYP monooxygenases* (human *CYP2C8*, *CYP2C9*, *CYP2C19*, and *CYP2J2*) in normal human colon cells (CCD-18Co) and human colon cancer cells (HCT-116 and Caco-2) ( $n = 3-4$  per group). (B) Western blotting analysis of CYP2C9 expression in normal colon cells and colon cancer cells. The results are expressed as mean  $\pm$  SEM. The statistical significance of two groups was determined using Student's *t* test or Wilcoxon-Mann test.



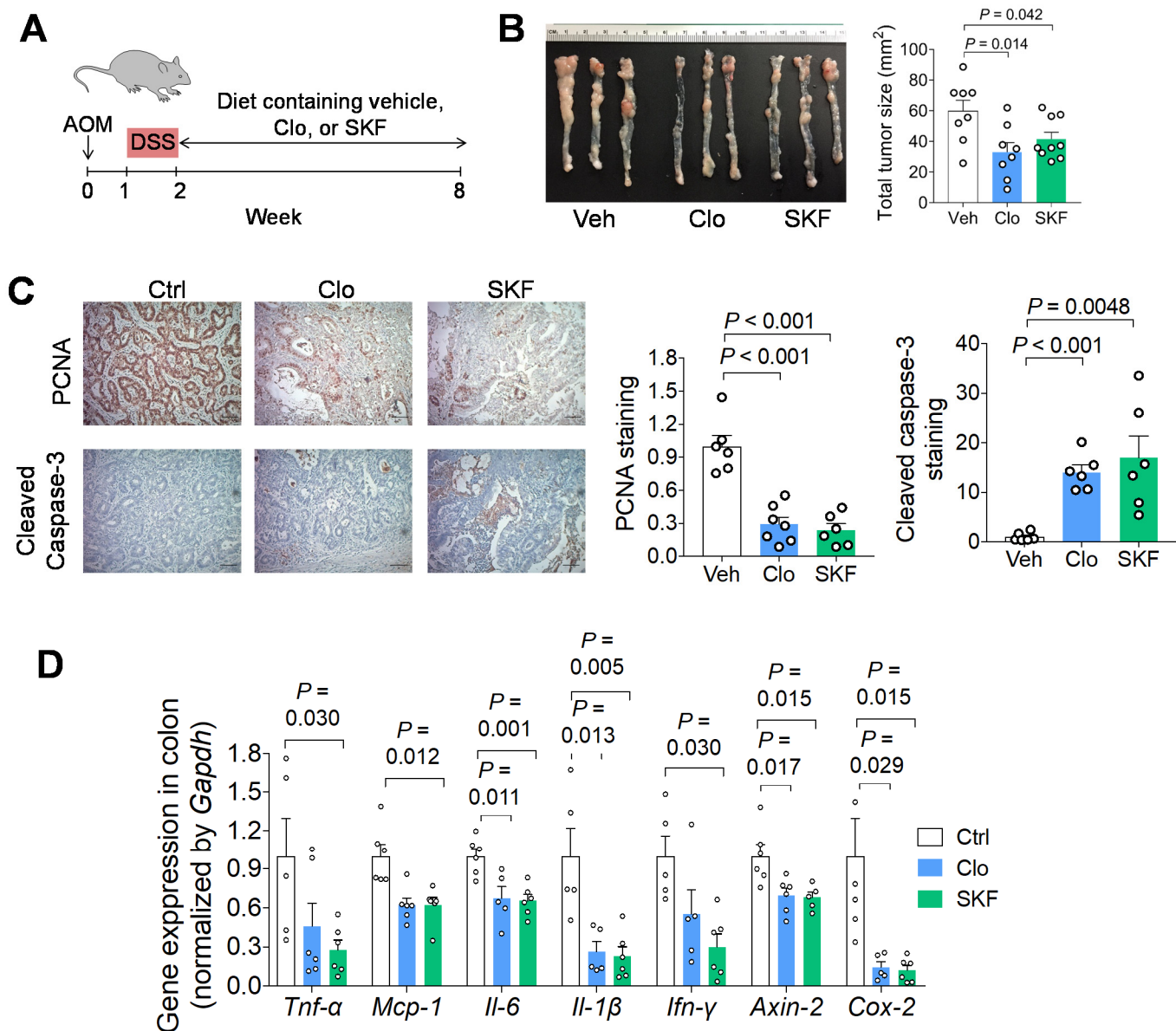
**Figure S2.** Gene expression of *Cyp2e1* in the liver of *Cyp2c*<sup>+/+</sup>, *Cyp2c*<sup>+/-</sup>, and *Cyp2c*<sup>-/-</sup> mice (n = 5-7 per group). The results are expressed as mean ± SEM.



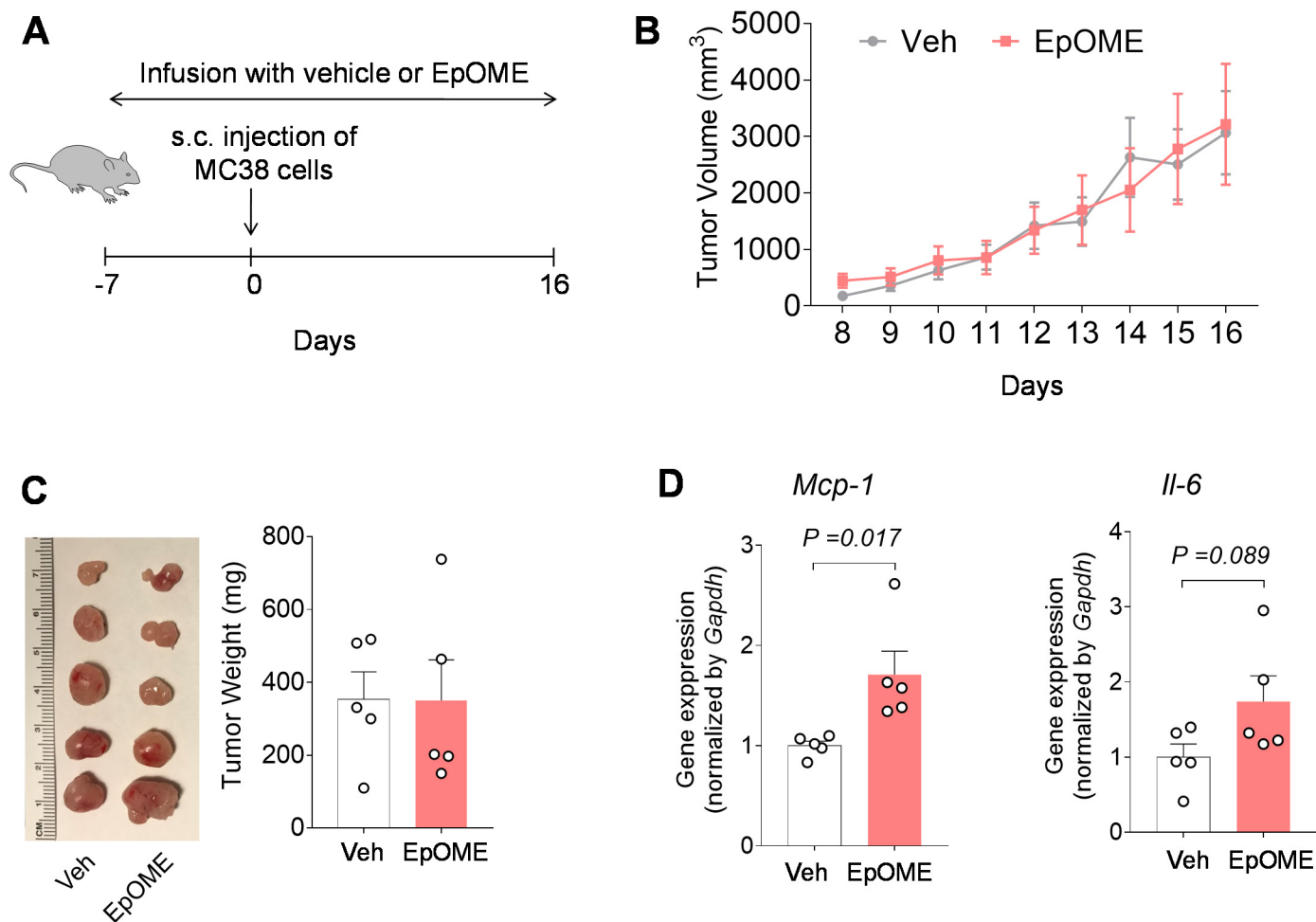
**Figure S3.** Compared with *Cyp2c*<sup>+/+</sup> mice, the *Cyp2c*<sup>+/-</sup> mice showed little signs of basal inflammation, but the *Cyp2c*<sup>-/-</sup> mice had severe liver inflammation. (A) Gene expression of pro-inflammatory cytokines (*Tnf-α* and *Il-1β*) in the liver of *Cyp2c*<sup>+/+</sup>, *Cyp2c*<sup>+/-</sup>, and *Cyp2c*<sup>-/-</sup> mice (these mice were under normal condition, without any treatment) (n = 6-7 per group). (B) H&E histology of the liver of *Cyp2c*<sup>+/+</sup>, *Cyp2c*<sup>+/-</sup>, and *Cyp2c*<sup>-/-</sup> mice (scale bar: 50 μm). The results are expressed as mean ± SEM.



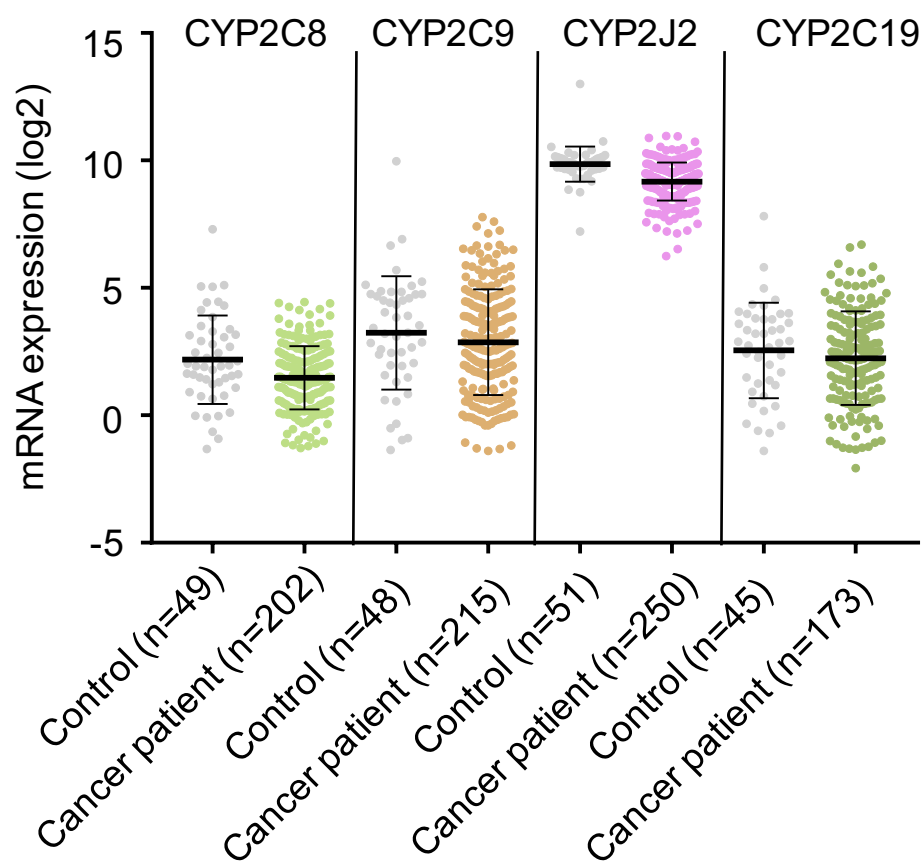
**Figure S4.** Survival curve of the AOM/DSS-stimulated *Cyp2c*<sup>+/+</sup>, *Cyp2c*<sup>+/-</sup>, and *Cyp2c*<sup>-/-</sup> mice. (Top panel) Scheme of animal experiment, (Bottom panel) survival curve. When the *Cyp2c*<sup>-/-</sup> mice were stimulated with AOM/DSS, there was a rapid animal death within 1-3 days post the DSS treatment (6 out of 8 *Cyp2c*<sup>-/-</sup> mice died during this period); in contrast, all of the *Cyp2c*<sup>+/+</sup> and *Cyp2c*<sup>+/-</sup> mice survived during the whole experiment. The statistical analysis of survival was determined using log-rank (Mantel-Cox) ( $P = 0.0143$ ) test and Gehan-Breslow-Wilcoxon test ( $P = 0.0177$ ).



**Figure S5.** Pharmacological inhibition of CYP monooxygenases suppresses AOM/DSS-induced colon tumorigenesis in mice. (A) Scheme of animal experiment. (B) Quantification of colon tumorigenesis (n = 8-9 per group). (C) Immunohistochemical staining of PCNA and cleaved caspase-3 in the colon (n = 6-7 per group, scale bar: 50  $\mu$ m). (D) Expression of pro-inflammatory and pro-tumorigenic genes in the colon (n = 5-7 per group). The results are expressed as mean  $\pm$  SEM. The statistical significance of two groups was determined using Student's t test or Wilcoxon-Mann test. Abbreviations: Clo: clotrimazole; SKF: SKF-525A.



**Figure S6.** Effects of 12,13-EpOME on MC38 tumor growth in C57BL/6 mice. (A) Scheme of animal experiment. (B) Tumor sizing. (C) Tumor weight. (D) Expression of pro-inflammatory genes in tumors. The results are expressed as mean  $\pm$  SEM,  $n = 5$  per group.



**Figure S7.** mRNA expression levels of *CYP monooxygenases* in control subjects and colon cancer patients. All the data were derived TCGA database through Firebrowse (<http://firebrowse.org/>).